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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/628,415	07/29/2003	Ludger Johannes	2121-0176P	6282

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EXAMINER	
MINNIFIELD, NITA M	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
10/31/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/628,415	JOHANNES ET AL.	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 25-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *27* is/are allowed.

6)☒ Claim(s) *1-8,25,26 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicants' amendment filed October 23, 3007 is acknowledged and has been entered. Claims 9-24 have been canceled. New claims 27 and 28 have been added. Claims 1-8 and 25-28 are now pending in the present application. All rejections have been withdrawn in view of Applicants' amendment to the claims and/or comments, with the exception of those discussed below.

2. Claim 27 is allowable.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-8, 25, 26 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haicheur et al 2000 (J. Immunology, 2000, 165:3301-3308) in view of Wang et al (WO 95/11998) and Eichner et al (5994311).

Haicheur et al teaches a construct of the B subunit of Shiga toxin fused to a tumor peptide (abstract). The prior art teaches that the Shiga B subunit acts as a vector (i.e. carrier) (see abstract; p. 3301, col. 2). Haicheur et al teaches that the "Shiga B subunit targets this pathway in a receptor-dependent manner, namely via binding to the glycolipid Gb3. Because this receptor is highly expressed on various dendritic cells, it should allow preferential targeting of the Shiga B subunit to these professional APCs. Therefore, the Shiga B subunit appears to represent an attractive vector for vaccine development due to its ability to target dendritic cells and to induce specific CTL without the need for adjuvant." (abstract) Haicheur et al teaches that different peptides and proteins (i.e. OVA, SL8, P815A and P1A) can be fused to the Shiga B subunit (materials and methods, p. 3302, col. 1).

Haicheur et al teaches the STxB subunit and Z(n) wherein the Z can be a polypeptide (i.e. tumor peptide). The prior art does not teach the cysteine residues.

However, it is well known in the art to add cysteine residues to synthetic peptides for polymerization. Wang et al teaches that extra residues can be added to the ends of the SSAL (structured synthetic antigen libraries) and that KKK can be added at the amino terminus to increase peptide solubility, cysteine can be added to facilitate directed coupling to carrier molecules, and methionine can be added for cyanogen bromide cleavage if necessary. Wang et al teaches that the SSAL can be a domain within a peptide or can have other antigenic, diagnostic or therapeutic sites attached to it. The SSAL can be attached to a core sequence for facile delivery. These core sequences include branched cores, which can be an amino acid or an amino acid analog having two amino groups and one carboxyl group, each group capable of forming a peptide bond linkage. Preferably such amino acids are lysine or a lysine analog such as ornithine (see p. 20; p. 23). Wang et al teaches that "…SSAL can also be used to form conjugates, i.e., the SSAL, either in branched or linear form can be coupled directly or indirectly, by methods known in the art, to carrier proteins such as bovine serum albumin (BSA), human serum albumin (HSA), or to red blood cells or latex particles." (p. 21, lines 13-19) Eichner et al teaches that the groups capable of coupling can be present on the carrier and the peptide, but they can also be introduced by activating a reactive group in the molecule. Common reactive functions are, for example, the amino (NH.sub.2), imino (imidazol ring), hydroxyl (OH), sulphohydryl (SH) or carboxyl (COOH) groups. An advantageous method used in accordance with the invention is to

couple peptides provided with a carboxy terminal cysteine to the carrier molecule (BSA), after that has previously been activated with the sulpho-SMCC linker (col 6).

Since the prior art teaches that carriers (i.e. STxB, BSA, HSA etc) can be coupled directly or indirectly to a polypeptide and that the cysteine is added to facilitate coupling it would have been obvious to a person of ordinary skill in the art to combine to teachings of Haicheur et al in view of Wang et al to prepare a composition comprising the formula a STxB-polypeptide-cysteine (STxB-Z(n)-cys) for the purposes of targeting molecules to Gb3. The specification teaches that B-subunit of *Shigella dysenteriae* is an homopentamer protein (5B--fragments) and is responsible for toxin binding to and internalization into target cells by interacting with the glycolipid Gb3 found on the plasma membranes of these cells (p. 1, l. 11-14), which is what the prior art teaches. The claimed invention is prima facie obvious in view of the combined teachings of Haicheur et al in view of Wang et al and Eichner et al, absent any convincing evidence to the contrary.

Further, Wang et al, teaches that the cysteine can be added to facilitate directed coupling to carrier molecules. Because this concept is taught in the art, there is a reasonable expectation of success of making the claimed composition having the claimed formula, since Wang et al teaches that coupling the cysteine can be added to facilitate coupling to the carrier. Applicants and Haicheur et al use the STxB subunit for the same purpose of targeting molecules to Gb3. With regard to Applicants assertions regarding whether the cysteine is added to the N-terminus or C-terminus of the peptide, it is noted that Eichner et al teaches that you can couple peptides for

example at carboxyl groups. Therefore it would have been obvious to a person of ordinary skill in the art at the time the invention was made to optimize the formula for the composition by using the terminus that provided a better universal polypeptidic carrier. It would have been obvious to one having ordinary skill in the art at the time the invention was made to couple the cysteine to the terminus (N- or C-) that does not alter the function of the carrier, since it has been held that discovering an optimum components of a composition are only routine skill in the art. *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980). The claimed invention is prima facie obvious in view of the combined teachings of Haicheur et al in view of Wang et al, absent any convincing evidence to the contrary.

Applicants have asserted that the Examiner has focused only a single sentence of the reference (brief single disclosure showing that cysteine residues can be added to synthetic peptides in order to facilitate the directed coupling of the peptides to the carrier) and has ignored the rest of the teachings as a whole and that picking and choosing only those parts of a reference to render this rejection is contrary to the law. However, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, Wang et al teaches that cysteine residues can be used to facilitate binding of a peptide to a carrier. Wang et al teaches that cysteine can be added at the amino terminus of the protein to facilitate directed coupling to the carrier molecules (p. 20; see also p. 21).

The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." In re Heck, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting In re Lemelson, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)). A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). See also Celeritas Technologies Ltd. v. Rockwell International Corp., 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir. 1998) (The court held that the prior art anticipated the claims even though it taught away from the claimed invention. "The fact that a modem with a single carrier data signal is shown to be less than optimal does not vitiate the fact that it is disclosed.").

Further, the rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). See also In re Kotzab, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) (setting forth test for implicit teachings); In re Eli Lilly & Co., 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) (discussion of reliance on legal precedent); In re Nilssen, 851 F.2d 1401, 1403, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988) (references do not have to explicitly suggest combining teachings); Ex parte Clapp, 227 USPQ 972

(Bd. Pat. App. & Inter. 1985) (examiner must present convincing line of reasoning supporting rejection); and Ex parte Levengood, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993) (reliance on logic and sound scientific reasoning).

It is noted that the claims recite that Z is an amino acid and that n is 0, 1 or a polypeptide. With regard to Haicheur et al, it would appear that the teaching of a portion of ovalbumin (nine amino acid residues of ovalbumin) would constitute a polypeptide.

Applicants' arguments have been previously addressed. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., length of peptides that bind to B subunit of Shiga toxin; maintain a functional structure in order to be active; specific size, geometric shape and charge; location of cysteine coupling to Shiga B toxin) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is noted that although the prior art may not specifically set forth an example using cysteine, the prior art does teach that cysteine can be used; the lack of a specific example does not render the reference non-enabling.

The rejection is maintained for the reasons of record. Applicant's arguments filed October 23, 2007 have been fully considered but they are not persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., additional cysteine residue would not alter the structure of the Shiga toxin B subunit in such a way that its carrier would not be greatly affected) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e. additional cysteine residue that targeting to the GB3 receptor cells was not modified) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event

a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert B. Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO

Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/N. M. Minnifield/
Primary Examiner,
Art Unit 1645
October 27, 2008